PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/58, 31/165 — A1

(11) International Publication Number: **WO 00/53188**

(43) International Publication Date: 14 September 2000 (14.09.00)

(21) International Application Number: PCT/SE00/00418

(22) International Filing Date: 2 March 2000 (02.03.00)

(30) Priority Data:
9900834-4 9 March 1999 (09.03.99) SE

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TROFAST, Jan [SE/SE]; AstraZeneca AB, R & D Lund, S-221 87 Lund (SE). BAUER, Carl-Axel [SE/SE]; AstraZeneca AB, R & D Lund, S-221 87 Lund (SE).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NEW COMBINATION OF R,R-FORMOTEROL AND BUDESONIDE IN A PHARMACEUTICAL COMPOSITION USEFUL FOR TREATING RESPIRATORY DISORDERS, SUCH AS ASTHMA, RHINITIS AND COPD

(57) Abstract

The invention relates to novel combinations of medicaments useful in the treatment of mild, moderate and severe asthma and other respiratory disorders such as rhinitis and chronic obstructive pulmonary disease (COPD).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NEW COMBINATION OF R,R-FORMOTEROL AND BUDESONIDE IN A PHARMACEUTICAL COMPOSITION USEFUL FOR TREATING RESPIRATORY DISORDERS, SUCH AS ASTHMA, RHINITIS AND COPD

Field of the invention

This invention relates to improvement in the treatment of mild, moderate and severe asthma and other respiratory disorders such as rhinitis and chronic obstructive pulmonary disease (COPD). More particularly, it relates to the use of the steroidal anti-inflammatory drug budesonide in combination with the strongly active R,R-enantiomer (preferably as the fumarate dihydrate salt) of the long-acting bronchodilator formoterol (R,R;S,S) for the treatment of respiratory disorders such as mild, moderate and severe asthma, rhinitis and COPD, and to pharmaceutical compositions containing the two active ingredients.

Background of the invention

The recognition more than 10 years ago of the fundamentally inflammatory nature of asthma led to the suggestions that control of the underlying airway inflammation could provide the key to the control of asthma at all levels of severity. Nevertheless many patients with asthma of most levels of severity still receive no regular anti-inflammatory treatment and are treated only with intermittent or regular bronchodilator therapy. Prophylactic therapy is typically provided by steroids such as beclomethasone dipropionate (BDP), flunisolide, triamcinolone acetonide, dexamethasone, mometasone furoate, fluticasone propionate and budesonide or by way of sodium cromoglycate or nedocromil sodium.

Long-acting β2-agonists such as formoterol and salmeterol, have different properties from short-acting ones such as terbutaline and salbutamol. These long-acting bronchodilators have been regarded as add-on treatment to steroid therapy. However, the long-acting agonists are considered an alternative to a further increase in the dosage of inhaled steroids. The side-effects of the steroids could therefore be minimized. Therapy should be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for

treating the underlying inflammation. An interesting approach for this treatment strategy would be to combine a β2-agonist with fast onset of action for symptom control together with an anti-inflammatory agent like a glucocorticosteroid.

The most common cause for poor control of asthma is poor compliance in the long-time management of chronic asthma, particularly with prophylatic treatment such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β2-agonist inhalers, since these provide rapid onset of symptoms, but often do not take the prophylactic therapy, such as inhaled steroids, regularly because there is no immediate symptomatic benefit.

Drug stereoisomerism is increasingly being recognized as an issue having clinical, research and regulatory implications. Differences in the pharmaco-dynamic and pharmacokinetic properties of stereoisomers are well documented e.g. the pharmacological properties of drug enantiomers can be dramatically different; one isomer may be predominantly responsible for the desired therapeutic action and the other for the side effects. In the case of formoterol (a mixture of R,R and S,S), the R,R-enantiomer is about 1000 times more potent than the S,S-isomer (see Trofast et al (1991)).

Earlier mentioned combinations of long-acting β-agonists and steroids include the use of salmeterol/beclomethasone dipropionate (US 5,208,226, Glaxo), salmeterol/fluticasone propionate (US 5,270,305, Glaxo) and formoterol/budesonide (US 5,674,860, Astra). The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects.

Summary of the invention

It has now surprisingly been found that a combination of R,R formoterol and budesonide can be used for the treatment of respiratory disorders such as asthma, rhinitis and COPD. According to the invention there is provided a pharmaceutical combination which comprises R,R formoterol in combination with budesonide.

Detailed description of the invention

The present invention provides a novel combination therapy using the long-acting bronchodilator R,R-formoterol (preferably as the fumarate dihydrate salt) and the glucocorticosteroid budesonide.

In a first aspect the present invention provides a pharmaceutical combination which comprises:

(a) R,R-formoterol, or a pharmaceutical acceptable salt or solvate thereof,

(b) budesonide; and optionally

(c) one or more pharmaceutically acceptable additives, diluents or carriers;

Preferably the molar ratio of (a) to (b) is from 1:4 to 1:100.

The word "combination" is used to describe the invention because the components can be administered simultaneously or sequentially for use in therapy. Thus the active ingredients (a) and (b) are not necessarily, but may be, used as an admixture, they still have the desired effect if they are administered sequentially or separately. Preferably they are not administered more than about two hours apart, for example no more than 30 minutes apart.

The first main ingredient of the combination of the invention is the single enantiomer R,R-formoterol i.e. R,R-(N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methyl-ethyl]-amino]-ethyl]phenyl]-formamide, an adrenoceptor agonist which selectively

stimulates β2-receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by endogenous mediators, and increased mucociliary clearance. The compound can be prepared by methods described in "Large-Scale Synthesis of Enantio- and Diastereomerically Pure (R,R)-formoterol" by R. Hett et al. in Organic Process Research & Development, 2 (1998), 96-99 or in "Steric Aspects of Agonism and Antagonism at β-adrenoceptors: Synthesis of and Pharmacological Experiments With the Enantiomers of Formoterol and Their Diastereomers" by J. Trofast et al in Chirality 3 (1991), 443-450.

The other main ingredient is budesonide i.e. 16,17-butylidenebis(oxy)-11,21-dihydroxy-pregna-1,4-diene-3,20-dione. The compound can be prepared by the methods described in US 3,929,768. The compound exists as epimers, and either epimer can be used in the combinations of the invention, including the 22R epimer.

A combination, preferably a fixed combination i.e. given in admixture, of the compounds of the invention will establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies the life for the patients considerably and makes life more comfortable and secure.

According to another aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of R,R-formoterol (and/or physiologically acceptable salt and/or solvate thereof) and budesonide as a preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders such as asthma, rhinitis and COPD. Reference to formoterol and salts and solvates thereof includes all combinations of solvates and salts of formoterol such as solvates of salts.

The invention additionally relates to the use of R,R-formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of pharmaceutical compositions as preparations for simultaneous, sequential or separate

administration of R,R-formoterol and budesonide by inhalation in the treament of respiratory disorders such as asthma, rhinitis and COPD.

According to a further feature of the invention there is provided a method of treating respiratory disorders which comprises the simultaneous, sequential or separate administration by inhalation of effective amounts of R,R-formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

Suitable physiological salts of R,R-formoterol include acid addition salts derived from inorganic and organic acids, such salts as the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluene-sulphonate, methanesulphonate, ascorbate, salicylate, acetate, succinate, lactate, glutarate, gluconate, tricarballate, hydroxynaphthalenecarboxylate or oleate. R,R-Formoterol is preferably used in the form of its fumarate salt and as a dihydrate of that salt.

The intended dose regimen is once or twice a day, where the suitable daily dose of R,R-formoterol is in the range of from about 5 to about 250 nmol (preferably from about 10 to about 120 nmol) and for budesonide a daily dose of about 0.1 μmol to about 3 μmol with a preferred dose of about 0.1 μmol to about 2 μmol. The doses of R,R-formoterol to budesonide should be selected to be within the molar range of from 1:4 to 1:100. The two drugs may be administered separately in the same ratio. The dose of choice will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

The combination is inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler e.g. multidose reservoir systems from Astra (Turbuhaler®) or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs. A diluent or carrier, generally being non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will

give the medicament a certain taste can be added to the powdered medicament in an amount of from 50 μg to 25 mg per dose, more preferably in an amount of from 50 μg to 10 mg, most preferably in an amount of from 100 to 2000 μg.

One or more of the ingredients is preferably in the form of a dry powder, more preferably a micronized dry powder, morst preferably an agglomerated micronized dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse particles of the pharmaceutically acceptaible additive, diluent or carrier. A fraction of fine particles of carrier may also be present. The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art. The particle size of the active ingredients is less than 20 μm, preferably less than 10 μm.

When the ingredients of the system are adapted to be administered from a pressurized inhaler, they are preferably in micronized form. They are dissolved, or, preferably suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the ingredients of the system of the invention are adapted to be administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The invention is illustrated by the following examples which are not intended to limit the scope of the application. In the examples micronization is carried out such that the particle size range for each component is suitable for administration by inhalation. The dry powder

formulation containinig an additive, diluent or carrier could be either in agglomerated form or as ordered mixtures .

Example 1.	Per dose
R,R-Formoterol fumarate dihydrate	6 μg
Budesonide	100 μg

Example 2.	
R,R-Formoterol fumarate dihydrate	6 μg
Budesonide	200 μg

Example 3.	
R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	100 μg

Example 4.	
R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	50 μg
Lactose monohydrate	up to 0.5, 1,5,10,20 mg

Example 5.	
R,R-Formoterol fumarate dihydrate	3 μg
Budesonide	100 μg
Lactose monohydrate	up to 0.5, 1, 5, 10, 20 mg

Example 6.

R,R-Formoterol fumarate dihydrate	3 µg
Budesonide	200 µg
Lactose monohydrate	up to 0.5, 1, 5, 10, 20 mg

Example 7.

R,R-Formoterol fumarate dihydrate	3 µg
Budesonide	100 µg
Oleic acid (based on propellant)	0.005 %
Ethanol (based on propellant)	1.5 %
Propellant P134a	up to 25, 50 or 100 µl

Example 8.

R,R-Formoterol fumarate dihydrate	6 µg
Budesonide	200 µg
Oleic acid (based on propellant)	0.01 %
Ethanol (based on propellant)	1.5 %
Propellant P227/P134a (15/85)	up to 25, 50 or 100 µl

Example 9.

2.6 parts of R,R-formoterol fumarate dihydrate and 896.8 parts of lactose monohydrate were mixed in a tumbling mixer to an evenly distributed mixture, whereafter the mixture was micronized in a spiral jet mill using a pressure and feeding suitable to obtain a particle size of less than 3 um. The micronized particles were then treated using a method described in WO 95/05805 to remove amorphous regions in their crystal structure. 98 parts of micronized budesonide were added and the mixture was remicronized at a lower pressure in a spiral jet mill to a homogeneous mixture. The powder was then agglomerated by feeding into a screw feeder (K-tron), sieved, spheronized in a rotating pan, then sieved

again, spheronized once more before final sieving (0.8 mm mesh size) to give a powder suitable for an inhaler.

Example 10.

Example 9 was repeated with identical conditions but using 2.6 parts of micronized R,R-formoterol fumarate dihydrate, 798.8 parts of micronized lactose monohydrate and 196 parts of micronized budesonide.

Claims.

1. A pharmaceutical combination which comprises:
(a) R,R-formoterol, or a pharmaceutical acceptable salt or solvate thereof,
(b) budesonide; and optionally
one or more pharmaceutically acceptable additives, diluents or carriers.

2. A pharmaceutical combination according to claim 1 wherein the molar ratio of (a) to (b) is from 1:4 to 1:100.

3. A pharmaceutical combination according to claim 1 or 2 in which the R,R-formoterol is in the form of the fumarate dihydrate salt.

4. A pharmaceutical combination according to any one of claims 1 to 3 in which the combination is fixed and given in admixture.

5. A pharmaceutical combination according to any one of claims 1 to 4 in a form suitable for administration from a pressurised inhaler.

6. A pharmaceutical combination according to claim 5 comprising
R,R-formoterol, or a pharmaceutical acceptable salt or solvate thereof,
budesonide; and optionally
a propellant and one or more other surfactants and/or one or more excipients.

7. A pharmaceutical combination according to claim 6 in which the propellant is HFA 227.

8. A pharmaceutical combination according to any one of claims 1 to 7 for use for the treatment or prophylaxis of a respiratory disorder.

9. A pharmaceutical combination according to any one of claims 1 to 7 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00418

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/58, A61K 31/165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9815280 A1 (ASTRA AKTIEBOLAG ET AL), 16 April 1998 (16.04.98) --	1-19
A	CHIRALITY, Volume 3, 1991, Trofast, Jan et al, "Steric Aspects of Agonism and Antagonism at Beta-Adrenoceptors:" page 443 - page 450 --	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2000	07 -07- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/gh Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 00/00418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9815280 A1	16/04/98	AU 4578297 A	05/05/98
		BR 9706822 A	23/03/99
		CA 2239308 A	16/04/98
		CZ 9801761 A	16/09/98
		EP 0871450 A	21/10/98
		HU 9901674 A	28/09/99
		NO 982414 A	27/05/98
		PL 327037 A	09/11/98
		SE 9603669 D	00/00/00
		SK 75198 A	04/11/98